

REMARKS

I. Amendments To the Claims

Claims 1-16, 18-23 and 33-46 were canceled in the response filed on February 20, 2007. Claims 25 and 26 have been canceled without prejudice. Applicant reserves the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional application.

Claim 17 has been amended to recite inflammatory bowel disease or Crohn's Disease. Claim 24 has been amended to delete "antihistamine" and "anti-cancer agent," and to change "a patient" to "the patient." Claim 47 has been added. The support for the amendment is found at paragraph [0025] of the published application.

By the amendments, Applicant does not acquiesce to the propriety of any of the Examiner's rejections and does not disclaim any subject matter to which Applicant is entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1856 (U.S. 1997). Upon entry of the present amendments, claims 17, 24, 27-32 and 47 are pending in this application. No new matter has been introduced by the amendments, and their entry is respectfully requested.

II. Claim Objection

Claim 24 is objected to for an informality reason. Claim 24 has been amended to change "a patient" to "the patient," as the Examiner suggested. The objection is overcome in view of the amendment.

III. Claims Rejection under 35 U.S.C. §103

Claims 17 and 24-32 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,877,200 ("Muller"). Pages 3-5 of Office Action. Specifically, the Examiner alleges that Muller teaches a method for treating a variety of diseases associated with TNF- α , which comprises administering 3-(3,4-dimethoxyphenyl)-3-(1-oxo-isoindolin-2-yl)-propionamide. Page 3 of Office Action. It is also contended that Muller discloses that the compound may be administered in optical isomer forms. *Id.* Thus, the Examiner alleges that the instant claims are *prima facie* obvious over Muller. Page 4 of Office Action. Applicant respectfully disagrees.

In *KSR International Co. v. Teleflex Inc.*, the U.S. Supreme Court rejected the Federal Circuit's *rigid application* of the "teaching, suggestion, motivation" test ("the

TSM test”) in determining obviousness in the particular case in question. 127 L.Ed.2d 705, 82 U.S.P.Q.2d 1385, 1395 (2007) (emphasis added). According to the Supreme Court, the correct analysis is set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). *Id.* However, the *KSR* decision indicated that while the TSM test is not the sole method for determining obviousness, it may still be used and in some cases is helpful. *Id.* at 1396. (“When it first established [the TSM test], the Court...captured a helpful insight.”). Indeed, the guidelines for the examination of patents in the wake of the *KSR* decision make clear that an Examiner may still apply the TSM test, after resolution of the *Graham* analysis. See Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57526, 57528 (Oct. 10, 2007) (“USPTO Guidelines”).

The *Graham* factual inquiries are: (1) determine the scope and contents of the prior art; (2) ascertain the differences between the prior art and the claims at issue; (3) resolve the level of ordinary skill in the pertinent art; and (4) evaluate any evidence of secondary considerations. *KSR*, 82 U.S.P.Q.2d at 1395 (citing *Graham*, 383 U.S. at 15-17). Once the *Graham* factors have been addressed, the Examiner may apply the TSM test, asking whether (1) a teaching, suggestion or motivation exists in the prior art to combine the references cited, and (2) one skilled in the art would have a reasonable expectation of success. See USPTO Guidelines at 57534.

1. The PTO has failed to make a *prima facie* case of obviousness.

The *Graham* factual inquiries begin with determining the scope and content of the prior art. See USPTO Guidelines at 57527 (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005)). The instant claims recite, *inter alia*, methods of treating inflammatory bowel disease or Crohn’s Disease using a specific compound, enantiomerically pure (-)-3-(3,4-dimethoxyphenyl)-3-(1-oxo-isoindolin-2-yl)-propionamide. Muller discloses cyclic amides as TNF α inhibitors. However, Muller does not teach or suggest the use of enantiomerically pure (-)-3-(3,4-dimethoxyphenyl)-3-(1-oxo-isoindolin-2-yl)-propionamide for treating inflammatory bowel disease or Crohn’s Disease recited in the instant claims.

The scope of the instant claims, which recite the use of a specific enantiomer, is in stark contrast with the breadth and general teachings of Muller, wherein thousands of compounds are described. Specifically, Muller discloses two general

formulas (Formula I and Formula II), and three general formulas for preferred subclasses of each class (IA, IB and IC for I; IIA, IIB and IIC for II). The combinations of the various substituents in the formulas of Muller would lead to thousands of compounds. Muller does not provide one of ordinary skill in the art with any suggestion or motivation to single out the specific racemate to which the claimed isomer belongs. The mere fact that a species is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. MPEP § 2144.08; *In re Baird*, 16 F.3d 380, 382, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994); *see also In re Brouwer*, 77 F.3d 422, 425, 37 U.S.P.Q.2d 1663, 1666 (Fed. Cir. 1996) (the mere fact that one species selected from a genus could be modified or replaced to reach the claimed invention does not render the claims obvious unless the prior art suggested that modification or replacement)). While Muller discloses the racemic compound in Example 42, Muller provides no teaching, suggestion or motivation to select this compound, much less the specific stereoisomer from the many examples provided therein for the treatment of inflammatory bowel disease or Crohn's Disease.¹ Muller does not provide a "finite number of identified, predictable solutions," but a "broad selection of compounds any of which could have been selected as the lead compound for further investigation." *Takeda Chemical Ind., Ltd. v. Alphapharm Pty., Ltd.*, 429 F.3d 1350, 1356, 1359 (Fed. Cir. 2007). Therefore, there is no adequate support in the prior art for the selection of the recited compound to establish a *prima facie* case of obviousness. *Id.*

Furthermore, the use of a specific isomer can be patentably distinct from its racemate. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); and *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, 348 F.Supp.2d 713, 755 (N.D.W.Va. 2004). Even assuming, *arguendo*, that one skilled in the art would select the compound of Example 42, the Examiner has provided no teaching, suggestion or motivation to select the (-)-enantiomer of the compound recited in the instant claims. It is well known to those skilled in the chemical and pharmaceutical arts that the separation and/or preparation of specific enantiomers is not predictable, nor are these processes always routine. *See, e.g.*, J. Darrow, "The Patentability of Enantiomers: Implications for the Pharmaceutical Industry," 2007 Stanford Tech. L. Rev. 2, ¶56 ("the process for

¹ Many species of compounds are disclosed in Muller. *See, e.g.*, examples 1-101.

making the racemate may not make obvious a process for resolving the racemate.”). Also, whether a specific enantiomer has improved biological activity or a more desirable pharmacological profile is recognized as unpredictable in the art. *See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, at 754 (the prior art suggested unpredictability in the degree of activity exhibited by a specific enantiomer); *see also Ex Parte Bonfils*, 64 U.S.P.Q.2d 1456, 1461 (B.P.A.I. 2002).² Muller provides no teaching or suggestion for the biological or pharmacological activity of the instant enantiomer to treat inflammatory bowel disease or Crohn’s Disease. Thus, without such specific guidance in the prior art, one skilled in the art would have no motivation to select the specific enantiomer of the instant claims. Without such motivation, a *prima facie* case of obviousness cannot be made.

Finally, Muller provides no motivation for the treatment of inflammatory bowel disease or Crohn’s Disease with the specific enantiomer of the instant claims. Muller teaches that the inhibition of the production or action of TNF α provides a therapeutic strategy for alleviation of many inflammatory, infectious, immunological or malignant conditions, and these include a number of diseases (Column 3). This broad teaching can hardly be said to focus on the treatments of the instant diseases as the Examiner suggests. (Office Action, pages 3-4). Muller provides no teaching or suggestion of the instant methods for treating the specific diseases using the specific enantiomer of the instant claims. The PTO has failed to show with specific facts how one skilled in the art would be motivated to use one particular enantiomer to treat particular diseases within the instant claims from Muller. Without demonstrating why one skilled in the art would be motivated to make this specific selection, the instant claims cannot be obvious over Muller. *See KSR*, 82 U.S.P.Q.2d at 1395 (Examiner must “identify a reason that would have prompted a person of ordinary skill...to combine the elements in the way the claimed new invention does.”).

In other words, Applicant respectfully points out that the PTO bears the burden of establishing a case of *prima facie* obviousness against the claims as a whole. That is, all the claim elements must be considered in a 103 rejection. Muller does not disclose or suggest the use of the specific enantiomer for treating the specific diseases

² *Bonfils* (copy enclosed) is a nonprecedential decision.

as recited in the instant claims. Thus, for these reasons alone, a *prima facie* case of obvious cannot be made.

2. One skilled in the art would have no reasonable expectation of success to arrive at the instant claims in view of the reference cited by the Examiner.

Further, the reference cited by the Examiner does not suggest to one of ordinary skill in the art that the present invention would have a reasonable expectation of success. To have a reasonable expectation of success, “one must be motivated to do more than merely ‘vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave...no direction as to which of many possible choices is likely to be successful.’” *Medichem, S.A. v. Robaldo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (*quoting In re O’Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)). Furthermore, the courts have long recognized the unpredictability of biological properties of chemical compounds. *See In re Eli Lilly & Co.*, 902 F.2d. 943, 948 (Fed. Cir. 1990) (“we recognize and give weight to the unpredictability of biological properties...”); *see also Takeda*, 429 F.3d at 1361.

To the extent Muller directs one to experiment with thousands of cyclic amide compounds, Muller does not teach or suggest the selection of the enantiomerically pure (-)-3-(3,4-dimethoxyphenyl)-3-(1-oxo-isoindolin-2-yl)-propionamide within the instant methods. While Muller discloses that thousands of cyclic amide compounds are inhibitors of TNF- α , Muller does not teach or suggest the biological activity of the specific enantiomer to treat the specific disease inflammatory bowel disease or Crohn’s Disease within the instant methods. In view of the teachings of Muller, one skilled in the art would have no reasonable expectation that the selection of the enantiomerically pure compound recited in the present claims from many examples provided therein would be useful in treating inflammatory bowel disease or Crohn’s Disease. *See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, at 754 (N.D. W. Va. 2004) (the prior art suggested unpredictability in the degree of activity exhibited by a specific enantiomer); *see also Forest Labs., Inc. v. Ivax Pharmaceuticals, Inc.*, 438 F. Supp. 2d 479, 493 (D. Del. 2006); *Bonfils*, 64 U.S.P.Q.2d at 1461.

From the teachings of Muller, one skilled in the art would be required to “try each of numerous possible choices until one possibly arrived at a successful result” with absolutely “no direction as to which of many possible choices is likely to be

successful.” *Medichem*, 437 F.3d at 1165. This is precisely what the courts have held not to be a reasonable expectation of success. *See Id.*; *O’Farrell*, 853 F.2d at 903-04.

Because the Examiner has not demonstrated that one skilled in the art would have had a reasonable expectation of success in practicing the methods of the instant claims by Muller, the instant claims are not obvious over Muller.

3. There are sufficient unexpected results to rebut even a *prima facie* case of obviousness.

Further, even assuming, *arguendo*, a *prima facie* case of obviousness is established by the cited reference³, there is ample evidence within the present specification of unexpected or superior results for the activity of the recited enantiomer to rebut a *prima facie* case of obviousness. The specification of the present invention demonstrates that the specific enantiomer exhibits unobvious, unexpected or superior results in various experiments. As the Examiner is well aware, such unexpected results can rebut even a *prima facie* case of obviousness. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *see also In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-McNeil Pharmaceutical v. Mylan Laboratories*, 348 F. Supp. 2d 713, 755 (N.D. W. Va. 2004). Applicants invite the Examiner’s attention to the test results disclosed in the specification.

For example, the specific enantiomer of the instant claims surprisingly shows significant biological properties in inhibition of TNF α and PDE4, and the selectivity of PDE4 inhibitions.

Example 3 (page 41) of the specification of the instant application describes the effects of the instant claimed enantiomer in inhibiting production of pro-inflammatory cytokine TNF α , in LPS-induced TNF α production test. The experimental data showed TNF α IC₅₀ of 3 μ M for the claimed enantiomer, compared with TNF α IC₅₀ of 21 μ M for the racemic form. Thus, the specific enantiomer of the instant claims possesses unexpected superior effect in inhibition of TNF α .

Further, Example 4 (page 42) of the specification discloses the effects of the instant claimed compound in inhibiting PDE4. The experimental data showed PDE4 IC₅₀ of 4.4 μ M for the claimed enantiomer, compared with PDE4 IC₅₀ of 15 μ M for the racemic form. Thus, the claimed enantiomer possesses unexpected superior effect in

³ This statement is not to be construed as an admission, on the part of Applicants, regarding the teachings or suggestions (or lack thereof) of Muller.

inhibition of PDE4. Example 5 (page 42-43) of the specification describes the selectivity of the instant claimed compound in inhibiting PDE. The experimental data in Table II showed that compared with the racemic form, the claimed enantiomer possesses unexpected selectivity as a PDE4 inhibitor.

In addition, the claimed enantiomer also possesses unexpected superior pharmacokinetic properties. Example 5 (specification, page 42-43) compared the pharmacokinetic properties between the claimed enantiomer and the racemic form. The results in Table III illustrate that after oral administration, the claimed enantiomer reached a higher plasma concentration within a shorter period of time than the racemic form, and achieved larger AUC (area under curve) than the racemic form.

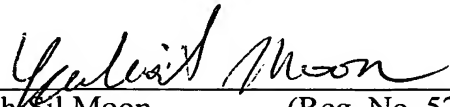
In sum, the unexpected superior effects of biological and pharmacokinetic properties of the claimed enantiomer are sufficient to rebut even a *prima facie* case of obviousness. In view of the unexpected results, the instant claimed invention is not obvious. *In re May*, at 1094; *In re Chupp*, at 646; and *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, at 755. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendments and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

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